CURCUMINOID-INSPIRED SYNTHETIC COMPOUNDS AS ANTI-TUMOR AGENTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a nonprovisional of and claims priority to U.S. Provisional Application No. 62/520,788 entitled "Novel Curcuminoid-Inspired Synthetic Compounds (with Potent Cytotoxicity and Anti-Proliferative Properties) as Anti-Tumor Agents", filed Jun. 16, 2017, the contents of which are hereby incorporated by reference into this disclosure.

FIELD OF THE INVENTION

The invention relates to antitumor agents. More specifically, the invention relates to a series of new CUR— and CUR—BF2 compounds with monocyclic aromatic and bicyclic-heteroaromatic lateral rings, bearing diverse substituents including fluorine(s), OCF3, CF3, and SCF3 groups (to increase polarity and lipophilicity), and their alpha-carbonyl-fluorinated analogs, as well as their pyrazole and isoxazole derivatives. The invention also relates to heterocyclic CUR—BF2 adducts and CUR compounds based on indole, benzothiophene, and benzofuran along with their aryl-pyrazoles.

BACKGROUND OF THE INVENTION

Parent compound curcumin 1 (FIG. **1**) is a non-toxic phenolic natural product. The central core of 1 is a conjugated β-keto-enolic moiety that can participate in hydrogen bonding, act as Michael acceptor, and coordinate to metal ions, while its hydrophobic phenyl domains are potential sites for π-π interactions with the aromatic side chains in amino acids, and the phenolic OH groups are capable of H-bonding interactions. (S. C. Gupta, et al., *Nat. Prod. Rep.* 2011, 28, 1937-1955).

Combination of these structural features, and its ability to influence multiple signaling molecules made it very challenging to unravel the biological profile of CUR and to identify its pharmacophore, despite extensive studies aimed at improving its pharmacokinetic profile and potency. (A. Minassi, et al., *J. Nat. Prod.* 2013, 76, 1105-1112; K. Bairwa, et al., *RSC. Adv.* 2014, 4, 13946-13978; A. Vyas, et al., *Curr. Pharm. Des.* 2013, 19, 2047-2069).

Whereas potential health benefits of 1 and its anti-cancer, anti-inflammatory, antioxidant and anti-mutagenic effects are extensively studied and documented, unfavorable bio-physicochemical features namely poor solubility, low absorption, low bioavailability, and rapid metabolism have so far prevented the development of a CUR-based anti-cancer drug. (G. R. Pillail, et al., *Cancer Letters* 2004, 208, 163-170; A. L. Loprestil, et al., *J. Psychopharmacology* 2012, 26, 1512-1524; D. Perrone, et al., *Experimental and Therapeutic Medicine* 2015, 10, 1615-1623; K.-L. Tan, et al., *ChemMedChem* 2012 7, 1567-1579).

To address these shortcomings, extensive research has focused on synthesis of structurally modified CURs. These included changes in the aryl substitution patterns, synthesis of unsymmetrical CUR compounds by introducing two different aryl groups, introduction of diverse substituents at the central methylene carbon, as well as more drastic structural modifications such as converting the 1,3-diketone moiety to prazoles and isoxazoles, or complete deconstruction to monocarbonyl derivatives in order to prepare CUR mimics. These highly diverse structural modifications and their biological activity outcomes were summarized in a 2014 review. (K. Bairwa, et al., *RSC. Adv.* 2014, 4, 13946-13978). Considering drug delivery aspects, encapsulation into water-soluble hosts, conjugation with nanoparticles, polymeric micelles, or liposomes have been explored as possible methods to deliver curcumin to cancer cells. (M. Mimeault, et al., *Chin. Med.* 2011, 6, 31; C. Cheng, et al., *RSC Adv.* 2017, 7, 25978-25986; L. Zhang, et al., *Environ. Tox. Pharm.* 2016, 48, 31-38; M. M. Yallapu, et al., *Colloids and Surfaces B: Biointerfaces* 2010, 79, 113-125; J. Liu, et al., *Curr. Pharm. Des.* 2013, 19, 1974-1993).

Structural modifications have included introduction of enaminone, oxime, and dienone, and replacement of the central moiety with pyrazole and isoxazole rings. (D. Simoni, et al., *Biorg. Med. Chem. Lett.,* 2008, 18, 845-849; K.-L. Tan, et al., *ChemMedChem,* 2012, 7, 1567-1579; C. L. Nieto, et al., *Molecules,* 2015, 20, 15643-15665; M. W. Amolins, et al., *Bioorg. Med. Chem.,* 2009, 17, 360-367; M. Labbozzetta, et al., *Chem. Biol. Interact.,* 2009, 181, 29-36; R. Narlawar, et al., *ChemMedChem,* 2008, 3, 165-172). It is noteworthy that many of these synthetic modifications represent significant departure from CUR's original skeleton. Other studies have reported improved bioactivity by transforming the phenolic OH in CUR to acetates and amino acid conjugates, cinnamic and succinyl esters, other types of esters, and acetamides. (S. B. Wan, et al., *Int. J. Mol. Med.,* 2010, 26, 447-455; L. Feng, et al., *Chem. Pharm. Bull.,* 2015, 63, 873-881; W. Wichitnithd, et al., *Molecules,* 2011, 16, 1888-1900; Z. Cheikh-Ali, et al., *ChemMedChem,* 2015, 10, 411-418; R. Sribalan, et al., *Bioorg. Med. Chem. Lett.,* 2015, 25, 4282-4286). Introduction of ester or α, β-unsaturated ester linkers into the active methylene region has been used to prepare curcuminoid libraries as potential antitumor agents for lung and prostate cancer. (K. Wada, et al., *Bioorg. Med. Chem.,* 2015, 23, 1507-1514; L. Lin, et al., *Bioorg. Med. Chem.,* 2006, 14, 2527-2534; L. Lin, et al., *J. Med. Chem.,* 2006, 49, 3964-3972).

Studies of heterocyclic curcuminoids have so far mainly focused on systems in which the diketo-linker was replaced with piperid-4-one, tetrahydrothiopyran-4-one, or terahydropyran-4-one moieties. There are also limited examples in which phenyl rings were replaced with thiophene, pyrrole, or pyridine, while maintaining the 1,3-keto-enolic structural motif. Synthetic progress along with the pharmacological properties of these compounds have been reviewed. (M. Martinez-Cifuentes, et al., *Curr. Topic. Med. Chem.* 2015, 15, 1663-1672).

Selective fluorine introduction into pharmaceuticals is a powerful strategy for improving metabolic stability and physiochemical properties, but this approach has remained greatly under-utilized with respect to curcuminoids. (J. Wang, et al., *Chem. Rev.,* 2014, 114, 2432-2506; H.-J. Bohm, et al., *ChemBioChem,* 2004, 5, 637-643).

Since the standard approach for the assembly of symmetrical CUR analogs is via a "double aldol" condensation of aldehydes with acetylacetone, ring fluorinated derivatives can be synthesized via this route, however very few examples have been reported, and with limited NMR data. (E. V. Rao, et al., *Indian. J. Pharm. Sci.,* 2011, 73, 262-270; B. W. Megna, et al., *J. Surg. Res.,* 2017, 213, 16-24; S. Elavarasan, et al., *Journal of Chemistry,* 2013, 1-8; (a) S. Padhye, et al., *Pharm. Res.,* 2009, 26, 1874-1880; (b) S. Padhye, et al., *Pharm. Res.,* 2009, 26, 2438-2445).

Examples of curcuminoids bearing a single fluorine at the active methylene position (along with an ester linker or a methyl group) have been very rare. (L. Lin, et al., *Bioorg.*